reduced the threshold for microwave induced damage to 0.26 W/kg (below the ANSI Safety Standard). In the latest extension of this study the pulse shape was found to be critical where a sharp rise-time was more effective in creating lesions irreversible in the retinal endothelium. The electroretinogram response to light stimulation was also depressed by microwave radiation which typically involved 4 h exposures on three consecutive days.

SAR measurements in human tissue phantoms in the brain and cheek have been shown to exceed the ANSI uncontrolled safe exposure levels. Furthermore, modelling studies have shown that for cellular telephones operating at the level of occupational standard the SAR in the pregnant fetus has been shown to exceed the uncontrolled level.

Problems in studies of human populations published to date include imprecise estimates of exposure. As a result such epidemiological studies may underestimate any real risk. The likelihood of epidemiological studies providing useful information is questionable, particularly if the biological endpoint cannot be predicted. Its value in the short term (< 10 years) must be negligible unless there was an enormous increase in the rate of cancer growth. Interestingly, the incidence of brain tumours in the EC countries has increased substantially in recent years. This fact has not escaped the attention of the media and implications of a possible connection with EMR were given in a recent commentary on television in the UK (June 1994).

Safety of RF radiation cannot be assessed in the absence of reported serious effects when so little research has been aimed at the problem. It is somewhat surprising and rather disappointing, to find that although the literature contains many hundreds of publications, there are very few areas of consensus. Where very high power outputs are emitted there are predictable effects related to tissue heating. The magnitude of effect, and hence the threshold in terms of SAR, varies according to the size of the animal so that considerably lower values apply to humans compared with rodents. At low levels the absence of clear thresholds and presence of intensity and frequency windows has created questions rather than provided answers.

The equivocal nature of much of the literature is of concern. Following discussions with a number of prominent researchers insight into the situation has been somewhat clarified. It seems that in the past the subject of EMR bioeffects has suffered from; (a) lack of direction, (b) poor dosimetry (as the

resolution of current numerical techniques were not available, (c) research studies based largely on the availability of equipment and biological systems within a particular organisation, i.e. no real attempt to predict a mechanism of interaction and match dosimetry, frequency and biological endpoint, (d) poorly described techniques, (e) obviously poor standard of peer-review, if any.

In many respects, the effects of exposure to RF from cellular telephones should be relatively easy to determine because the radiation is emitted from the antenna close to the skull. Although the field becomes complicated due to interference by the head, numerical methods to estimate local SAR are improving. Values for the maximum power outputs are available and a number of studies are investigating the SAR levels expected in various adjacent tissues. *In situ* SAR values on the order of 3 W/kg averaged over 10 gm of tissue have been estimated in brain tissue close to a cellular telephone operating at 900 MHz and maximum output. Under the same conditions the maximum SAR value averaged over 10 gm of tissue was 4.6 W/kg at 1.8 GHz.

It is difficult to envisage an epidemiological survey that would effectively discriminate amongst the other environmental variables, including the many forms of EMR that exist in addition to cellular telephone or telecommunications frequencies. As a number of cellular responses have been associated with low level (50-60 Hz) mains frequency, this may also be a potential confounding variable. The development of cancer is a slow process taking many years before it is positively diagnosed in humans. The latency factor is very important in evaluating cancer development. It is most unlikely that retrospective studies will provide any useful information for recently developed technology, such as cellular telephones. Prospective studies will have negligible chance of showing any effect, if present, in less than 10-20 years (Coleman 1994).

Concern over the lack of appropriate research was voiced by Frey (1988) in a chapter on evolution of research with low intensity ionizing radiation. At that time he somewhat outspokenly claimed that, "the significant research, that which does not use high intensities and is not thermoregulatory oriented, has been largely squeezed out for reasons unrelated to science." His concern was that while there is no doubt that there is a diversity of biological effects of low intensity RF radiation the research to evaluate and understand these processes is not being undertaken, at least in the USA.

There is no doubt that the interpretation of bioeffects data has been clouded by a pre-occupation with thermally-mediated processes. In fact, development of the ANSI/IEEE standard is based only on well established thermal effects, and ignores the more subtle non-thermal processes that are more difficult to interpret and apply to human health. The inappropriate exemption from standards by the 7W exclusion clause is due to be removed from the ICNIRP standard.

### 2.1.1 Implications

Because of its equivocal nature, the data base for RF emissions has limited value. It may be dangerous to make general statements on safety based on lack of evidence of harmful effects when so little relevant research has been carried out. The enhancement of ocular effects including corneal lesions by the simultaneous application of the glaucoma drug and very low SAR is a surprising finding. This has important implications to human health, and research into the mechanism of action is essential.

A common thread throughout much of the literature is the potential development of cancers. From a public health perspective, it would be appropriate that the main goals of such a study would be to identify mechanisms and demonstrate their capability to create biochemical/biomolecular changes that lead to altered gene expression. Studies that do not address the issue of mechanisms have a limited use for assessment of human health effects. However, bioeffects studies, *per se*, are necessary to establish threshold levels for interactions.

There are two approaches that can be taken to answer the problem of whether or not EMR can be linked with cancer or tumour promotion. A simplistic engineering response would be to take the view that any biological changes that cannot be explained by known mechanisms cannot be significant. The alternative view is to adopt the notion that existing knowledge on biological processes is inadequate and to work towards understanding these events and the potential risk with abnormal cellular development.

Currently a few laboratories are addressing the issue of signal transduction pathways from the cell membrane to the nucleus and the ultimate expression of altered genes. The role of highly reactive free radicals in carcinogenesis is under examination. The hormone melatonin is a potent antioxidant and, therefore, could protect DNA against damage and potential cancer promoting actions of free radicals. It has been shown that during EMR exposure melatonin secretion can be suppressed and the life of free radicals is significantly extended. Furthermore, free radicals are usually produced during the intracellular signal transduction process that follows response to EMR exposure.

Cancer related phenomena require long term studies, and only parts of the signal cascade of events are understood (or in most cases theorised). The solution to

the problem will not be achieved in the short term. Research on the mechanism for cancer production has been extensively funded for decades without elucidating an answer. In contrast, research on effects of EMR on cell membrane and gene expression are carried out under limited funding.

## 2.2 RECOMMENDED RESEARCH

There is an urgent need for an orchestrated research effort to combine rigorous animal experimentation and specialised bioeffects/mechanistic studies at the cellular and molecular level. It is essential that the biological aspects of EMR are thoroughly investigated to establish whether a mechanism exists by which carcinogenesis or cancer promotion may occur.

An effective research program will establish threshold levels for the onset of biologically significant events, from the level of molecular biology to whole organ systems and whole-being physiological reactions. Only when a solid data base of independently verified quantified bioeffects is available will meaningful safety standards be developed and reassurance of the public be achieved.

When safety of RF from sources other than cellular telephones is considered, the situation becomes more complex. The developing world of wireless networks will ensure that the entire body is radiated from multiple sources. An individual operating a terminal will be exposed to high GHz microwave radiation in addition to the electric and magnetic fields associated with the VDT. From the perspective of public concern, there is an emphasis on the need for credible data on risk to pregnancy. Much of the research on teratogenic effects involves high power exposures and resulting abnormalities and fetal resorptions that are known to be due to whole body hyperthermia in rodents.

An appropriately sensitive endpoint for low level chronic exposures would be the study of fetal brain development. There are specialised procedures available including embryo culture techniques that have been used to study non-thermal effects of non-ionizing radiation. Changes in brain tissue of developing or adult mammalian systems are not easily recognised but may occur with RF exposure. Intriguing effects on memory function in rats exposed acutely to 0.6 W/kg SAR have been reported. Current information is that this exposure also produces DNA breaks at SAR 0.6 to 1 W/kg.

The potentiation of effects on the CNS or sensory organs by pollutants or medication needs to be addressed. The recent reports of substantial lowering of the threshold for microwave-induced corneal lesions (2.6 to 0.26 W/kg) by administration of a glaucoma drug emphasises the difficulties in this area. All

other ocular effects are obviously and predictably, due to temperature increases in the lens. Research is urgently needed to substantiate these reports and identify the mechanisms involved.

Studies involving chronic exposures are most relevant to RF radiation environment. These should continue to study the effects on tumour promotion and sensory and cognitive function.

Tests of learning performance are an essential part of a research program. The potential synergistic effects of drug therapies needs to be evaluated. At the cellular level studies should include verification of the response of ionic flow and activation of ion channels in the bilipid membrane.

Work at a subcellular level should include study on biochemical process, particularly on enzyme systems such as ornithine decarboxylase, that control growth function and have a connection with tumour development. Studies on the potential RF-induced expression of oncogenes are an important basis for cancer-related effects. The effects of microwave radiation on cell proliferation, reproduction and transformation are fundamental to the study of tumour development and require sustained and thorough investigation.

**For Australia to have an effective role** in the human health consideration of EMR requires the establishment of:

(1) an **expert committee** to critically evaluate dosimetry and bioeffects of published studies that will emanate over the next few years of increased funded research,
(2) **strategic liaisons** that allow direct lines of communication with the research, regulatory, and political community,
(3) **research protocol** for critical areas of research,
(4) **international collaboration** to verify important studies.

To avoid the risk of introducing preconceived prejudices the best line of action would be to have a small committee direct appropriate research in an organised manner. It should be capable of identifying relevant expertise and applying the resources to specific topics and problems. If care is taken in this approach it should be possible to get relevant research carried out in a meaningful way to ensure unbiased results. By selecting individual expertise it is possible that a systematic approach can be used to develop a research protocol that holds no political bias and has a strong chance of producing definitive results. A study

that ultimately provides benefit to Australia by producing information that is directly relevant to human health should be favoured. With the current status of international research in EMR there is clearly an opportunity to make a valuable contribution.

The Recent recommendation (September 1993) by the International Union of Radio Science (URSI), Commission K, is as follows;

## *URSI Seeks Health Research on Wireless Communications*

*The resolution reprinted below was adopted by Commission K on Electromagnetics in Biology and Medicine at the International Union of Radio Science (URSI) meeting in Kyoto, Japan, in September. It was later ratified by the URSI Council, according to Commission K chairman Dr. Paolo Bernardi of the Department of Electrical Engineering at the University "La Sapienza" in Rome, Italy. Commission A is on electromagnetic meteorology. Commission B is on fields and waves.*

Commission K. *Considering,*

(a) That there is a rapid development of new technologies such as wireless local area networks (LANs), cellular phones, low-earth-orbiting satellites (LEOS), communication networks (e.g., Iridium), personal communication services (PCS), cordless telephones and other devices, and their wide spread is anticipated;
(b) That there exists scientific uncertainty about potential impact of electromagnetic fields from wireless communication on human health;
(c) That there is public concern about health effects of all electromagnetic devices;

*Recommends* that broad-based research programs should be established nationally and internationally to address the key issues, namely:
1. What are the interaction mechanisms of weak electromagnetic fields of various characteristics with living systems;
2. What biological effects and particularly potentially harmful effects are caused, and under what exposure conditions;
3. How to evaluate the exposures through proper measurements and dosimetric modeling.

The Commission gratefully acknowledges the promised support of Commission A in the area of the measurements and Commission B in the area of the dosimetric modeling.

## 2.3 OVERVIEW AND GENERAL DISCUSSION

There have been sporadic reports of biological effects of exposure to EMR at frequencies relevant to telecommunications, however there has been no deliberate direction of this research towards an evaluation of health effects, to date. The nature of competition for research grants has limited fundamental research of new ideas. This is obvious from the lack of follow-through of some early studies that indicated potential effects. Industry is the largest provider of funds for research and this has its inevitable consequences in terms of acceptance of the results as being truly without bias. By far the largest funding continues to be directed towards research on ELF. The emphasis on EMR research in the USA is still on safety of power lines. The Department of Energy and Power Companies continue to invest heavily in research on ELF. Recently this has been stimulated by epidemiological reports from Scandinavia associating ELF with leukemia. There have been very few studies aimed at establishing physical mechanisms of interaction for biological effects of EMR, particularly for low-level exposures. Reports of effects at very low levels of exposures in both ELF and RF have emanated from eastern Europe. This continues to be the case. It is uncertain why these studies should contain such high sensitivity but the general opinion is that they are treated with some degree of scepticism.

Effects on cellular processes that have been reported may seem somewhat esoteric at first sight. Some are implicated in tumour development by alteration in enzyme activity and biochemical processes that control DNA replication, transcription, and the rate of cell division. The movement of calcium ions across cell membranes alters its concentration within cells where it provides an essential regulatory role in cell growth and behaviour, thus ionic flow across membranes is important. The cell membrane itself is an efficient and sensitive receptor organ that reacts to minute changes in its chemical and physical environment. The chemistry of cell growth and behaviour is clearly affected by the electrical and magnetic environment. While the biochemical processes in cell kinetics are reasonably well understood, the mechanism of interaction by EMR is mostly speculative. Cell membrane ion-channels, gap junction intracellular communications all play an important role that may be mediated through the action of free radicals or melatonin.

In the search for sensitive biological responses to EMR it is understandable that a great deal of emphasis is placed on reactions at the cellular level.

There is some evidence of responses to low level amplitude-modulated microwave and radiofrequency radiation. Reported effects include changes in brain activity, increased enzyme activity and resulting altered rates of cell growth and proliferation, and reduced lymphocyte cytotoxicity. Taken as a whole, these biological effects are suggestive of developing neoplastic pathology. There have been reports from *in vitro* studies describing enhanced rates of cell transformations following exposure to amplitude-modulated microwaves at SARs up to 4 W/kg when combined with the chemical cancer promoter tetradecanol-phorbol-acetate (TPA). The cell line used in these experiments was chromosomally abnormal and the validity of extrapolating from such a specialised experimental procedure to human health, may be questioned.

The problem with the approach taken by organisations such as ANSI and IRPA or ICNIRP is that the data on which their standards are based come from relatively severe physiological reactions. Interference with normal behaviour is taken as a robust indicator of a response that is repeatable and which occurs throughout a range of species at exposure levels of around 4 W/kg. A so-called safety margin factor of ten is included to set the occupational level at 0.4 W/kg (ANSI 1990). Clearly, the fact that the response is so repeatable suggests that its stimulus is strong enough to always evoke a response. The alteration in normal behaviour is based on an increase in the mean body temperature by at least 1°C, measured in the rectum. Temperature increases in the CNS were not estimated but it would not be surprising if localised hyperthermia occurred. A change that overcomes the homeothermal control mechanism and elevates the temperature of the whole body to an extent that it interferes with normal behaviour, including feeding, certainly represents a substantial effect.

It appears that the standards organisations prefer to base their standards on gross physiological responses initiated by significant temperature increases. It is, perhaps, more difficult to correlate a direct human health effect with the more sensitive cellular responses that cannot be easily explained by thermal mechanisms. The problem is that the Standards imply safety thresholds but it is not possible to identify these on the basis of current equivocal or disparate research.

The main concern about the ANSI and IRPA standards is that their selection criteria restricts the data base to reports of thermally-mediated effects from a single, i.e. acute, exposure to a single source. The Australian Standard is similar and also includes an exemption for devices emitting frequencies below 1 GHz

and powers of less than 7 W. It is odd that cellular telephones should be exempted when they represent a unique device that operates with its transmitter placed against the user's head.

## Cancer

There is no evidence that low levels of electromagnetic radiation at frequencies up to 300 GHz can directly alter the DNA genetic material of cells and initiate cancer. However, there is some evidence that EMR alters enzyme synthesis in ways similar to known chemical cancer promoters. There is some evidence that microwave radiation influences the transport of calcium through cell membranes, stimulates the synthesis of ornithine decarboxylase within cells and may alter the expression of DNA synthesis by cells, thereby, promoting more rapid development of malignant cells *in vitro* and of tumours in animals. There is evidence from *in vitro* studies that these effects can be produced under conditions where heating is unlikely to be involved. Some of the reported bioeffects of EMR are not proportional to dosage, and the reported "windows" of intensity and frequency present a challenge to scientific understanding and explanation. Although EMR is not considered to be capable of initiating neoplastic pathology there is a limited data base suggesting that EMR may promote the growth of malignancies, particularly when initiated by a chemical or physical agent.

Past chronic exposure animal studies have produced conflicting results, with one study (Chou et al 1992) giving either a positive or a negative result depending on whether one interprets a real effect as; (1) an increased incidence in all cancers in the population, or (2) an increased incidence of a specific cancer.

Exposure protocols need to be strictly controlled. If there is the smallest risk of enhancing cancer promotion then experiments should be designed to optimise their statistical power. Apart from the obvious need to control all environmental variables this involves testing for a modest increase in the incidence of a known cancer from chronic exposure (daily, throughout life) to a known RF field that can be quantified as an *in situ* SAR. It is well accepted that *in situ* dosimetry is significantly altered by orientation with respect to the field. The worst-case situation occurs when the animal's body is parallel to the electric field, particularly in the MHz frequency range. The exposure conditions must involve a worst-case situation which is constantly repeatable to have any real value in determining thresholds. There is little value in radiating rodents that

are free to move about when the *in situ* SAR is strongly dependent on their orientation in the RF field. Comparison of results of biological effects must take account of differences in species and microwave frequency, in addition to SAR, as resonant conditions relate directly to the size of the animal relative to the wavelength.

True scientific protocol requires the establishment of an hypothesis which must be repeatedly tested before any inference can be drawn from the results. The *in vitro* cell studies have provided some clues about setting such hypotheses. Perhaps the most important were the experiments of Cleary et al (1990 a) which demonstrated an altered rate of DNA synthesis and proliferation of human glioma cells after a single exposure to microwave radiation. This abnormal behaviour is consistent with early changes seen in cells that lead to tumour formation. Effects were observed at both 27 and 2450 MHz frequency and with cw or pulsed waveforms. Furthermore, Cleary (1990 b) also reported the effect in cultured human glioma cells. The exposures were applied over a range of SAR, with the lowest level at which the effect was observed being 5 W/kg. Although the exposure conditions have been reported as non-thermal it is difficult to see how the exposure could avoid large thermal gradients from the cells to the cooling fluid surrounding the cell culture vessel.

What makes these studies interesting is that the effect occurs after a single 2 h exposure and lasts for up to five days. Thus, a daily exposure regimen would reinforce the effect. This is what is required in the promotion phase of cancer development. The connection between accelerated growth of human brain tumour cells in culture to that occurring *in vivo* during repeated exposure to EMR is one that deserves close examination. Hence the need for data from chronic animal studies. The extrapolation of results from laboratory rodents to humans is always fraught with difficulties and divergent opinions. Epidemiology studies may be an option, although the cost/benefit ratio may not be acceptable, and scientists are frequently sceptical of the results.

The transformation of normal cells into malignant neoplasms involves alterations of the nuclear DNA and its genetic code This can be induced by physical agents such as ionizing radiations or chemical promoting agents such as the phorbolester tetradecanol-phorbol-acetate (TPA). This chemical promoter apparently acts on receptor molecules in the cell membrane thereby triggering a specific calcium-dependent and lipid-dependent protein kinase enzyme system,

protein kinase C. Another effect of TPA is the synthesis in cells of ornithine decarboxylase, an effect that has also been reported after exposure to microwaves.

Most serious researchers concede that the bulk of the scientific literature is of a poor standard. This has lead to some concerned scientists establishing working groups. A non-ionizing radiation sub-committee of the IEEE (Chair Prof. M. Meltz) is currently working towards establishing an expert scientific committee that will critically review publications. It is intended that the critiques will be available, although the means by which this will be achieved is not determined. Because of concerns of litigation it is probable that it will be through personal communication. It is recognised that many publications (including those frequently cited) have significant inadequacies in the descriptions of dosimetry and biological protocol.

**Comment**

It is evident that, at least in the world of EMR, science has become a business, as evidenced by the growing number of environmental and epidemiological consultants. This is prevalent in the USA but also exists in the UK. The danger with this approach is that there is a tendency to adjust the research to fit the needs of the industry providing the funding. The scientific value of many of the science entrepreneurs may be questioned, as first principles of "where can I do my best science" are replaced by "where can I get funded". Meanwhile, epidemiology may be considered to be more of an art-form with the added bonus that it deals with "environmental" issues that are currently politically attractive.

The annual BEMS conference attracts a large number of posters and presentations that are not reviewed. This results in a wide range in quality and the format does not allow an opportunity to identify valid data. The danger here is that it is easy to assume that the general standard is poor (and indeed many presentations were quite inadequate) and, therefore, disregard most of the positive effects as being probably due to experimental artefact. This subject is in desperate need of a true workshop to identify areas of scientific consensus. It will require a dedicated effort by strong-willed individuals to break the mould of mediocrity that currently prevails.

## 2.4 TOPIC SUMMARY AND CONCLUSIONS : BIOLOGICAL EFFECTS OF EMR-TELECOMMUNICATIONS FREQUENCY

### 2.4.1 Human Studies

*Heating*

Healthy people can tolerate an elevated body temperature of 1°C for periods of less than 1 h, during which an increase in sweating, skin blood flow and cardiac output occurs. A SAR of 1 W/kg would be expected to result in a rise in body temperature of approximately 1°C in healthy subjects at rest in light clothing and in moderate environmental conditions. Adverse environmental conditions and moderate physical exercise will reduce the tolerable level of SAR, as would some medication or compromised thermoregulation.

Whole-body SARs provide no information about responses to high, localised SARs induced by specific exposure conditions or by high peak amplitude pulses. Furthermore, the relationship between local SAR and temperature increase is not clearly established.

*Perception*

RF and microwave radiation can be perceived audibly and by temperature receptive sensors in the skin. There are no specific thresholds of skin perception because of their dependence on frequency, exposure duration, the sensitivity of the part of the body exposed, and on the area exposed. Because of the greater penetration at lower frequencies, perception of skin warming by microwave and RF frequencies in the range of 0.5 - 100 GHz is not a reliable mechanism of protection against potentially harmful exposure.

People with normal hearing are capable of perceiving pulse-modulated RF radiation between 200 MHz and 6.5 GHz as audible buzzing, clicking, hissing or popping noise, depending on modulation characteristics. It is generally accepted that the sound results from the thermoelastic expansion of brain tissue following a small but rapid increase in temperature on absorption of the incident energy. The perception threshold for pulses shorter than 30 μs depends on the energy density per pulse, rather than an averaged value, and has been estimated as about 400 $mJ/m^2$ (≈ 15mJ/kg). Reports of altered EEG in humans exposed to RF radiation are equivocal, probably due to the difficulty of avoiding field perturbations and measurement artefacts.

### 2.4..2 Animal studies

*Ocular effects*

The lens of the eye is considered to be sensitive to RF radiation because of its lack of a blood supply (and consequent limited cooling ability), limited damage repair capability, and its tendency to accumulate damage and cellular debris. Local temperature increase, induced by RF exposure is responsible for the production of cataracts (opacities) in the lens of anaesthetised rabbits. The most effective frequencies are in the range of 1-10 GHz. The threshold temperature is 41-43°C with a corresponding local SAR 100-140 W/kg. Primate eyes were shown to be less susceptible to heating by microwaves than rabbit eyes, possibly due to the greater shielding by the primate skull and the thinner lens. Cataracts have not been produced in conscious primates after chronic exposure to power density up to 1.5 $kW/m^2$.

Recent, well-conducted, studies by one research group show the retina, iris and corneal endothelium of primates to be susceptible to low level pulsed microwave radiation. The latest report identified pulse shape as an important parameter where pulses with a sharp rise-time were most effective in producing damage to the retina and in depressing electro-retinograms at SAR 2.6 W/kg within the eye. Degenerative changes in the iris and cornea were observed at localised thresholds of 0.26 W/kg after the application of timolol maleate, a glaucoma drug. The energy level per pulse was 2.6 mJ/kg. This important finding requires verification by an independent research group.

*Haematology and immunology*

Reported effects are usually transient, resulting from acute, thermally-significant exposures. Small, transient changes may be of little consequence in the long-term. A common response was a decrease in peripheral lymphocyte count and an increase in the neutrophil count in mice and rats exposed at 5 - 13 W/kg and 1.5 - 3.0 W/kg, respectively; sufficient to raise the rectal temperatures by 1°C. However, several other authors reported no effect on circulating blood cell count in rats exposed at up to 2.5 W/kg. These inconsistencies, may be due to differences in dosimetry estimates and environmental conditions which would alter the induced temperature effects.

Changes in natural killer cell and macrophage activity were reported after acute exposure of hamsters at SARs = 13 W/kg or mice at SARs = 21 W/kg with an associated increase in rectal temperature of several degrees. An increase in the

primary antibody response of B- lymphocytes was reported in rodents exposed to levels above 5 W/kg. An increase in immune response has been reported (BEMS 1994 meeting, not yet published) in male mice after 7 daily exposures to 2.45 GHz, cw or pulsed at SAR of 0.14 W/kg. A transient change was also reported in the responsiveness of B- and T- lymphocytes to specific mitogens after 13 months of exposure in a life-time (27 months) radiation study on rats at SAR up to 0.4 W/kg (all other haematological indicators were normal; plasma corticosteroid levels were unchanged). The acute exposure of primates and rats to RF radiation at SARs of 3-4 W/kg, sufficient to raise rectal temperature by 1-2°C, resulted in elevated plasma corticosterone levels.

*Teratogenic effects*

Elevated body temperature is teratogenic to a number of mammalian species including primates. Thus, RF- or microwave-radiation-induced maternal hyperthermia is teratogenic in animals. In these studies, species differences and the use of different environmental conditions have led to some inconsistencies. Exposure at 11 W/kg raised the maternal temperature to 43°C in rats and induced embryonic and fetal death and developmental abnormalities. At 6-7 W/kg fetal growth retardation and postnatal behavioural changes occurred. Exposures below 4 W/kg generally had no adverse effect. Similar effects were described in mice, but at higher SARs. In addition, one study reported that while exposure at 4-5 W/kg produced no direct effect, it increased the effectiveness of a known chemical teratogen.

Irrespective of the SAR, substantial birth defects occur when the core temperature of the pregnant mother is increased by more than 2.5°C. Exposures that increase the maternal temperature by 1 - 2.5°C generally do not result in structural malformations but may significantly increase the incidence of abortions and resorptions, result in lower fetal body weight, or alter the behaviour of the exposed offspring. Non-specific stress during pregnancy is associated with reduced fetal and birth weight.

Recent studies reporting retarded embryonic development following acute or chronic exposure of avian embryos to low SAR (0.05 W/kg) at 428 MHz implicate a non-thermal mechanism that is, as yet, unexplained.

*Heating*

The most readily understood and accepted bioeffects data apparently result from an increase in tissue or body temperature of 1°C or greater. Most of these responses have been reported at SARs above 1-2 W/kg. However, differences in size and thermoregulatory ability preclude direct extrapolation of threshold SAR values from laboratory animals to humans. For a given temperature increase the required SAR value is substantially higher for small animals. Therefore, data from mice may underestimate the heating effect in humans.

*Cancer-related studies*

*In Vivo*

There is a lack of clear evidence for a mutagenic or carcinogenic effect of RF radiation. In a study of chronic exposure of rats from 2 months to up to 27 months of age at SARs of up to 0.4 W/kg the total incidence of neoplasia (benign and malignant) or of specific cancers was not increased. However, the total number of primary malignancies in the exposed group was significantly larger than in the controls. An earlier study looked for both spontaneous production and promotion of cancers. Chronic microwave exposure of mice at 2-8 W/kg was reported to result in an SAR-dependent increase in the progression or development of spontaneous mammary tumours or chemically-induced skin tumours. Another study showed that repeated exposures at 4-5 W/kg followed by the application of a non-carcinogenic dose of a known carcinogen to the skin, resulted in a three-fold increase in the number of skin tumours. These observations need replicating and extending. However, a great deal of care is required in developing the experimental design in such a way that provides for a realistic assessment of *in situ* dosimetry and which minimises the effects of stress.

Studies are currently in progress to evaluate; (a) the potential promotion of cancer (primarily brain tumours) in rats exposed chronically to cellular telephone frequency and absorbed dose, (b) the possible increase in incidence of tumours in a strain of mice genetically predisposed to lymphomas.

*In Vitro*

Some *in vitro* studies have implied a role for microwave exposure in cancer induction. Enhanced transformation rates were observed in cells exposed to combined amplitude-modulated microwaves (4.4 W/kg) and X-rays followed by

treatment with the chemical promoter TPA, compared to cells exposed only to X-rays and TPA.

Similar effects were reported in a further study when exposure to microwaves and/or X-rays (1.5 Gy) was followed by treatment with the chemical cancer promoter TPA resulting in a dose-dependent induction of neoplastic transformation. Microwave exposure also slightly enhanced the effects of X-irradiation and TPA on transformation rate. Transformation studies can be susceptible to experimental confounding factors, and the human health implications of data from chromosomally abnormal C3H10T$^{1}/_{2}$ cells for carcinogenesis *in vivo* is uncertain. Future studies should examine the responses of normal cells and animal models. Evidence that low level amplitude-modulated microwave radiation changes the intra-cellular levels of ornithine decarboxylase, an enzyme involved in tumour promotion, suggests that further research is necessary.

*Genetic studies*

There is no evidence from acute or chronic exposures to microwave radiation that shows an increase in mutation or chromosome aberration frequency in male germ cells at normal physiological temperatures. There is no verified report from studies using chronic, low level exposures (1-5 W/kg) of dominant lethal mutations in mice or rats. There is no confirmed evidence that RF or microwave radiation has clastogenic effects on somatic cells.

*Reproductive cells*

The testis is a heat-sensitive organ and is normally maintained at several degrees Celcius below body temperature. Male germ cells (particularly during meiosis) are known to be adversely affected by elevated temperatures. Chronic RF exposure at about 6 W/kg has produced transient infertility in male rats where the irradiation caused the rectal or testicular temperature to rise by 1.5-3.5 °C. Transient reduction in fertility is relatively minor compared to either accelerated, abnormal growth of germ cells (and possible genetic consequences), or retarded development after fertilisation.

*Nervous system responses*

Exposure to very low levels of amplitude modulated RF or microwave radiation has been reported by several groups to alter brain activity, measured by electroencephalography (EEG), and to affect calcium mobility in chick brain tissue *in vitro*. Effective SARs *in vitro* were less than 0.01 W/kg. The use of sophisticated techniques has recently allowed investigation of ion fluxes through

cell membrane channels. However, the reported RF-induced changes in calcium ion mobility have not been readily replicated. Models of nonlinear processes have been proposed including, power density and modulation frequency "windows". It has been suggested that the effects result from weak, co-operative interactions at the cell membrane. The physiological significance is not established although it is accepted that $Ca^{2+}$ concentration plays a major role in the regulation of cell processes.

RF radiation exposure can modify the action of drugs. The effects of low level RF radiation on the influence of neuroactive drugs, such as tranquillisers or stimulants, on EEG activity are variable. RF-induced altered permeability of the blood-brain barrier might affect the action of psychoactive drugs. The experimental evidence suggests that the acute exposure of conscious rats to microwave radiation at 13 W/kg, sufficient to increase brain temperature above 40°C, can alter the permeability of the blood-brain barrier.

*Learning impairment*

The threshold for disruption of conditioned behavioural responses in acutely exposed rodents is within the range 2.5 to 8 W/kg. The lowest threshold occurred with more deeply penetrating radiation. Impaired performance was also reported from chronic exposures to 2.45 GHz radiation at 2.3.W/kg. In all cases the mechanism appears to be thermal as colonic temperature was reported to increase by at least 1°C during irradiation. The acquisition of learned tasks is more sensitive to disruption with thresholds having been reported in the range 0.14 to 0.7 W/kg for chronic exposures to cw radiation at 2.45 GHz. Impaired short term memory function in rats has been repeatedly demonstrated (within the same laboratory) following acute exposure to 2.45 GHz at SAR of 0.6 W/kg.

### 2.4.3 CONCLUSIONS

Many of the biological effects of acute exposure to electromagnetic radiation are consistent with responses to induced heating of about 1°C, or more. Biological effects have been most reliably reported at SARs above 1-2 W/kg. Most animal data indicate that implantation and the development of the embryo and fetus are unlikely to be affected by microwave radiation which results in an increase in maternal body temperature by < 1°C. Such an exposure is not mutagenic and will not result in somatic mutation or hereditary effects.

Reports of non-thermal effects on cell and whole animal developing systems are inconsistent. Changes in phase transition temperatures in lipid cell membranes and consequent ionic fluxes during microwave radiation may offer clues to understanding the process of cell surface receptor and intracellular signal amplification.

The implications of reports of cell resonance effects at narrow frequency bands (or "windows") may have significance for molecular resonance in the GHz frequency range in specific telecommunication applications.

A number of research centres have planned, or have in-progress, chronic exposure studies to determine if radiation from cellular telephones can promote the development of cancers in rodents. Because of the complexities and expense of such studies none have so far been designed to study a dose-response. With the variability in species, exposure protocols, choice of primary carcinogen or co-promoter, there is a high probability that none of the studies will be exact replicates. As a whole-life study in rodents takes 2 - 3 years it will be some years before the data base shows any improvement from *in vivo* cancer studies.

Other *in vivo* studies that are capable of producing effects in the short term include; teratogenesis, interaction with the central nervous system, impaired memory function, and ocular damage from low level microwave exposures.

Research on these important issues may be more cost-effective and have a high probability of achieving useful information about human health. The cost-benefit ratio of epidemiological studies is arguably poor. An assumption is made that some form of cancer may result from RF exposure, although no accepted mechanism exists. The hypothesis is, at best, based on a weak association with ELF and cancer. Because of the long latency period for the development of human cancers a prospective study will require long-term study. The probability of achieving scientifically acceptable data is low.

## 2.5 PLANNED AND CURRENT RESEARCH

The investment of US $25 million by the CTIA is a clear admission of the need for a recognised research program. There are a number of other research programs in the US (at least two), Germany, France, of the order of US $2-3 million each. To be effective, the existing apparent haphazard approach to research on biological effects of microwave radiation needs to be directed. An effective central body should be able to establish an agenda that identifies the most directly relevant topics in a total research program. The CTIA has established a Scientific Advisory Group, and it is hoped that this body will go some way towards achieving such a goal, without prejudice. US researchers have been invited by CTIA to submit expression of interest (approx. 1 page description) for intended projects of bioeffects at CT frequencies. A selection process will invite full grant application by the end of 1994. It is evident that CTIA will select, and directly influence, research that it funds. Having attended the so-called "workshop on safety of cellular telephones", 13-17 June 1994 in Copenhagen, it seems that this might be unduly optimistic. In a presentation by George Carlo (Chairman of the CTIA Scientific Advisory Group), it was clear that there are considerable concerns about the way the program will be administered and conducted.

According to Carlo, peer review is important; therefore the "peer-review committee" (appointed by CTIA, or Carlo) will decide what studies to fund, it will peer-review the results of those studies and any publication will be reviewed by this selected group prior to submission to peer-review journals. This level of monitoring of the output is not surprisingly, treated with suspicion. It is difficult to perceive of truly unbiased data or interpretation arising from such studies.

The type of studies described by Carlo as important may not be the most appropriate. The use of "standard battery of toxicology tests" is appropriate when dealing with toxic chemicals but have unacceptably low statistical power for a cancer study that may involve a weak promoter where a dose response or reliable endpoint has not been established. His program has identified epidemiology studies as important, while the common opinion is that there is negligible chance of identifying a risk, certainly within the next 10 years. This issue was clearly put into perspective in a balanced presentation by Michele Coleman (BEMS 1994).

Similarly, the ideal of mechanistic studies is fine, but unlikely to achieve a result until verified bioeffects have been identified. There does not seem to be an agenda to fund studies on CNS effects and ocular damage that have been identified at low level acute exposures. However, the subject of CNS effects in animals and humans is planned in research programs in Germany (Telekom) and France (French Telecom Research Centre).

Because of the complexity of the subject there is an obvious need to develop a multi-disciplined team to undertake high quality research. One such centre is currently being established in San Antonio, Texas, where there exists a large diverse resource in facilities and personnel for *in vitro* and *in vivo* work, spread over a number of academic institutions and the US Air Force Base. A single facility that includes a wide range of expertise on a single campus exists in Loma Linda, California, although the work is primarily focused on ELF *in vitro* research. Much of the research in the microwave frequency range has been funded by the USAF. This includes studies within the USA and elsewhere, such as on numerical techniques for dosimetry at Kings College London. The USAF continues to contract out much of its research needs.

In the UK the LINK study, funded through the Department of Trade and Industry (DTI) involves a multicentre study with nine academic institutions and three commercial organisations. The emphasis is on computer modelling for dosimetry.

Part of the research program of the CSIRO Division of Radiophysics is the development of critical biological studies. One such program that would have benefit to the telecommunications industry, the CSIRO and Australia is the independent evaluation of thresholds (and the true dose-response) for microwave-induced ocular damage. It is also intended to study the teratogenic effects in specialised embryo culture conditions. CSIRO has local and international academic alliances that allow collaborative research on these and other vital topics. The frequency range will extend from cellular telephones to wireless PCNs.

# 3.0 ANIMAL STUDIES

Animal studies allow assessment of the potentially hazardous effects of physical or chemical agents on different body systems. The potential for adverse effects on reproduction and prenatal and postnatal development can be tested. The induction of mutagenic changes is important in the assessment of possible hereditary effects. Carefully controlled animal studies are an essential step in the extrapolation of biological effects to human health and safety.

## 3.1 OCULAR EFFECTS

### SUMMARY

The absorption of radiofrequency electromagnetic energy, particularly in the GHz frequency range, has been shown to result in damage to ocular tissues in experimental animal studies. The site of damage depends on the radiation frequency (related to depth of penetration) whereas the magnitude of effect primarily depends on the power density of the field, the quantity of absorbed energy and on the duration of exposure. The lens of the eye is susceptible to microwave and RF heating because of its lack of a blood supply and hence limited heat dissipating capability. Its constituent fibres have a limited capacity for repair and tend to accumulate the effects of minor insults.

Microwave induced temperature increase has been shown to produce cataracts in the lenses of anaesthetised rabbits. Microwave frequencies between 1 and 10 GHz are most effective in inducing lens cataracts. The threshold temperature for cataract induction from prolonged exposure (>100 mins) is 41 - 43°C, with a corresponding SAR of 100-140 W/kg resulting from exposure to power densities greater than 1.5 kW/m$^2$. Most experimental work on microwave induction of lens opacities (cataracts) has been carried out using near-field exposures at 2.45 GHz. The intense exposures used were generally far above perception threshold and the animals were normally anaesthetised. Cataracts produced in rabbits eyes are either caused by intense exposures sufficient to damage other ocular structures and rapidly produce opaque lenses or less severe exposures that result in posterior cortical opacities several days or weeks after exposure. The mechanism for cataract formation is considered to be thermal in origin.

Lens opacities have not been produced in the eyes of rhesus monkeys after acute exposures to 5 kW/m$^2$ (anaesthetised) or after chronic exposures of conscious monkeys to 1.5 kW/m$^2$. The difference in acute response may be due to

structural anatomical differences in the eyes and skull of rabbits and monkeys. Recent studies on monkeys have shown that other structures including the cornea and iris are susceptible to microwave radiations in combination with ophthalmologic drugs where the exposure levels are too low to involve a thermal mechanism. Well-conducted studies by a single research group (Kues et al 1992, 1994) have shown degenerative changes in the retina, iris and corneal endothelium of primates to be caused by low level microwave irradiation, particularly when pulsed. Localised threshold SARs were found to be as low as 0.26 W/kg when irradiated together with the glaucoma drug, timolol maleate. It is clearly important that these results are independently verified.

The apparent sensitisation of ocular tissues to microwave radiation by the application of a drug used in the treatment of glaucoma may provide evidence of a non-thermal effect. Timolol maleate normally offers protection to the eye against heat induced disruption of the blood aqueous barrier and the ocular temperature was said to have increased by less than 0.8°C at a SAR of 0.26 W/kg during the irradiation (Kues et al 1992).

The extrapolation of results of animal experimentation to human exposures is complicated by anatomical/structural differences in the head and eyes that result in different *in vivo* exposure conditions. Frequency and orientation dependent factors may have a significant impact on EM field distributions in the eyes of different species.

## Experimental Evidence

### 3.1.1 *Cataracts*

Posterior cortical cataracts have been reported to form within 1 week of exposure to 2.45 GHz radiation at approximately 4.2 $kW/m^2$ for 5 min or 1.5 $kW/m^2$ for 60 min (Carpenter 1979). The reaction varied from narrow translucent or milky bands in the posterior cortex that disappeared within a few days to permanent lesions. The extent of cataract formation varied with the power and duration of the exposure from a few fibrous "streaks" at the posterior suture to diffuse opacities.

The threshold power density for cataract formation in the rabbit eye by a single exposure of up to 100 min was calculated to be 1.5 $kW/m^2$ (Guy et al 1975). Based on temperature measurements in a dead animal it was estimated that the peak level of SAR occurred in the vitreous humour immediately behind the lens,

with a threshold for 100 min exposure determined to be 138 W/kg. Calculation of the heat flow within the rabbit eye predicted threshold temperatures at the back of the lens of 41 - 43°C, similar to the experimental data on temperature induced cataract formation in dogs. Induction of cataracts in the lens was shown to be heat-dependent when cataractogenic RF exposures applied to hypothermic rabbits failed to produce lesions (Kramar et al 1975). The existence of a thermal mechanism was given further support in a study that produced cataracts in rabbit eyes by heating the lenses above 43°C with circulating heated water.

Different results were reported in rhesus monkeys where 2.45 GHz radiation did not produce cataracts, even after exposure to power densities up to 5 $kW/m^2$ for 60 min (Kramar et al 1978). This is far above the threshold for cataract formation in the rabbit and sufficient to cause severe facial burns in the monkey. Peak temperatures occurred behind the lens in the monkey eye but were lower for a given exposure than those in the rabbit. Power densities of 2 and 5 $kW/m^2$ raised the retrolental temperature to 39 and 42°C, respectively. The different anatomical structure and size demonstrate important species differences. The extrapolation of results of animal experimentation to human exposures is complicated by anatomical/structural differences in the head and eyes that result in different *in vivo* exposure conditions.

Frequency and orientation dependent factors may have a significant impact on EM field distributions in the eyes of different species. It is well known that absorption of EMR by a lossy dielectric scatterer such as the mammalian head alters as a function of its shape and the applied frequency (NCRP 1986). It has been shown that (at 2.45 GHz) the measured field intensity at the position of the head of a rabbit was reduced by 40% by the presence of the animal in the field, and by a further 40% when its ears were fastened against its body (Carpenter et al 1974). In a comparison of the effects of 2.45 GHz radiation (Kramar et al 1978) cataracts were induced in rabbits but not in monkeys (table 3.1.1). These differences have been interpreted as being due to differences in field concentrations and heating of the lens.

The efficacy with which microwave or radiofrequency radiation can induce cataracts depends on the depth of penetration and hence on frequency. It has been reported that below 1.5 GHz the dimensions of the orbit-eye combination are too small to result in local field concentration (NCRP 1986).